FINAL REPORT – HILL v. SANOFI AVENTIS US INC. – September 11, 2009

Opinions

1) No immunological testing is recommended during Lovenox use.

2) No immunological studies concerning Lovenox have been provided discussing the immunogenic properties of Lovenox (enoxaparin) in-vivo or in-vitro.

3) The effects of Lovenox for exposure durations longer than 14 days are not adequately defined.

4) The safety and efficacy profiles of low-molecular-weight heparin (LMWH) use during pregnancy has not been evaluated adequately.

5) Heparin and LWMH are immunogenic and cause heparin induced thrombocytopenia (HIT).

6) All traditional causes of the present case of neonatal alloimmune thrombocytopenia (NAIT) were found to be inconclusive.

7) It is reasonable to believe that the present case of NAIT was caused by the effects of Lovenox administration.

Bases of Opinions

The opinions contained here are based upon relevant content in peer-reviewed scientific literature, scientific textbooks, medical records, and various depositions and testimony.

Heparin is a known immunogenic agent and can cause HIT, a serious condition. The development of IgG antibodies against complexes of heparin with platelet factor 4 appears to be responsible for HIT. These complexes activate platelets by binding to receptors, which result in platelet aggregation, release of more platelet factor 4, and thrombin generation.

The incidence of HIT is lower with LMWH, but not absent. Hence LMWH (including the LMWH Lovenox) can cause alterations in IgG levels, as evidenced by cases of HIT occurring during LMWH therapy. Even though HIT did not occur maternally in the present case does not mean that elevated IgG were not present maternally. To the contrary, positive indirect Coombs tests were observed, indicating free IgG in circulation.

The effects of long term Lovenox therapy during pregnancy have not been determined. It is reasonable to conclude that the effect of Lovenox therapy on IgG levels allowed excess maternally generated IgG to be transferred to the fetal circulation.

Maternal IgGs are important since they are the only antibodies which traverse the placental barrier and enter fetal circulation. The fetal/neonatal immune system is immature until the first several days following birth, and the only IgG source found in the newborn is from the mother. Normal IgG present in the fetus is an evolutionary protection for the fetus against infection during gestation. However, excessive fetal IgG levels can bind to fetal platelet blood cells and be taken out of fetal circulation, thereby causing thrombocytopenia.

Soon after birth, intravenous IgG and platelet therapies were initiated for Savannah so as to treat the evident NAIT condition. This therapy was found to be beneficial for Savannah. The over abundance of the infused IgG was able to saturate the spleen's IgG receptors and stop the fetal clearance of platelet-IgG complexes from the fetal circulation, while the platelet infusion therapy aided in building the platelet count back towards normal.

Dr. Weil, a neonatal hematologist, reviewed the medical case of Savannah Hill and provided testimony from her review. This review included many tests, and several etiologies for Savanah's NAIT condition were ruled out. The NAIT was concluded to be idiopathic. This is consistent with Lovenox as the causative agent for Savanah's NAIT. Dr. Weil was curious about the positive indirect but negative direct Coombs test results. The results of the direct and indirect Coombs tests supports Lovenox elevating IgG maternally, and then providing excess IgG across the placenta and then into the fetal circulation.

Lovenox was not expected to be given for long periods of time. No controlled clinical testing of Lovenox for periods longer than 14 consecutive days have been carried out.

The safety and efficacy profiles of low-molecular-weight heparin use during pregnancy have not been evaluated adequately. No studies during pregnancy have been conducted to determine the effects of Lovenox on pregnant individuals. Increased levels of IgG can arise maternally and remain relatively clinically asymptomatic. No blood tests were carried out to monitor such emerging conditions. It is well known that HIT can occur and can be easily diagnosed and would have been symptomatic to the mother. Conversely, gradual maternal IgG buildup can remain asymptomatic and sub-clinical. These manifestations can render this type of IgG buildup devastating in a pregnancy situation.

To date, no immunological studies concerning Lovenox have been provided which discuss the immunogenic properties of Lovenox (enoxaparin) in-vivo or in-vitro either during development or after launch of the product.

It is reasonable to assume that LMWH is immunogenic to a lesser extent than heparin, and can elevate IgG in the maternal circulation. Altered levels of maternal IgG from Lovenox treatment is transferred to the fetus while the mother remains clinically asymptomatic. The amount of IgG transferred to the fetal circulation increased and caused NAIT, which remained relatively asymptomatic until birth

Sincerely,

Eldon H. Nyhart, Jr., Ph.D.